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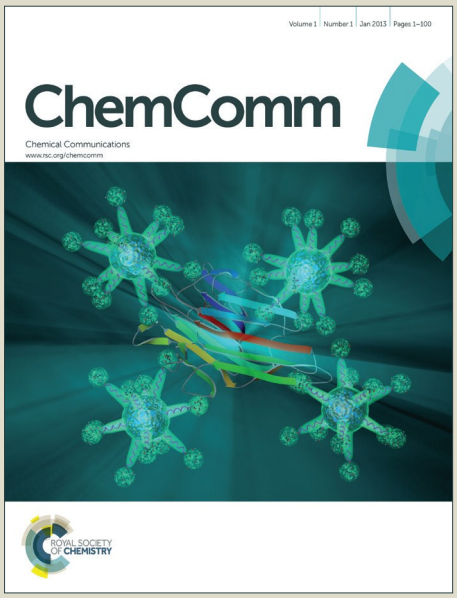

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Transition-metal-free Persulfuration to Construct Unsymmetrical Disulfides and Mechanistic Study of Sulfur Redox Process †

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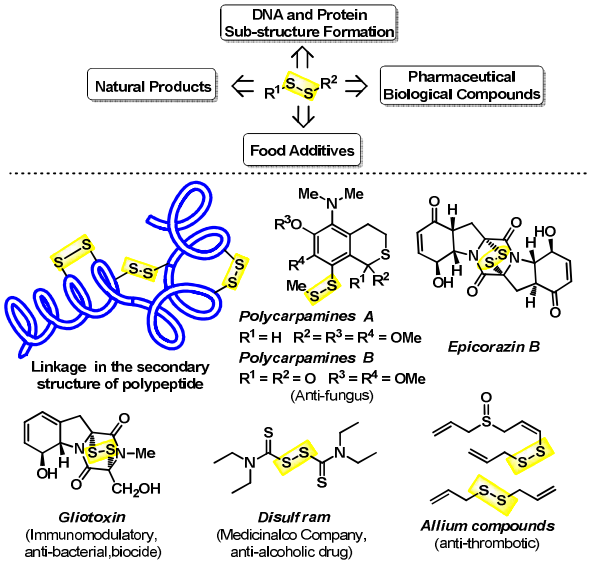
A sulfur redox process has been developed between sulfinate and thiosulfate, which efficiently affords diverse unsymmetrical disulfides and provides a new method to modify pharmaceuticals and natural products without requiring extra oxidant or reductant. Gram-scale investigation further demonstrates the practicality and application potential of this process. Isolated key intermediates and a series of control experiments afford an unusual process, which reveals the mechanism of comproportionation and the transition-metal-free sulfur redox process.

Disulfide bond, an important moiety, frequently appears in different types of significant organic molecules (Scheme 1). As a natural linkage, it partially determines the secondary and tertiary structure of polypeptide.[1] As a crucial motif, the S-S bond clearly plays an essential role in diverse activities of disulfide-containing natural products, such as anti-fungus of polycarpamine[2a] and anti-poliovirus/P. falciparum of epidithiodiketopiperazines (ETPs).[2b-e] In the field of drug discovery, disulfide has been shown to be a powerful anti-bacterial,[3a] anti-alcoholic,[3b] and anti-thrombotic[3c] reagent due to its potential to form sulfur radicals[3d] *in vivo*. Moreover, due to their characteristic function and smell, those compounds serve as food additives in some cases.[4]

Notwithstanding its great importance in numerous fields, effective methods for synthesizing unsymmetrical disulfide are quite rare. The classical methods (Scheme 2, eq. 1) affording unsymmetrical disulfide involved an S_N2 process,[5] in which prefunctionalized thiols with leaving group was utilized as one of the sulfur sources. An alternative approach subjected two different kinds of thiols under oxidative conditions, in which the homo-coupling byproducts were difficult to avoid (Scheme 2, eq. 2).[6] A particularly elegant strategy involved two different symmetrical disulfides undergoing an interesting exchanging reaction with the help of rhodium (I) to form unsymmetrical disulfide (Scheme 2, eq. 3).[7] The substrates of all of these methods were prepared from thiols, which were odorous, expensive, and difficult to access. In addition, the method to prepare



Scheme 1. Representative significant disulfide structures.

methyl unsymmetrical disulfides, which is known as a biologically important moiety, is still very limited.[5g, 5l-m, 8] Based on our own research, thiosulfate shows itself to be an efficient and unique inorganic sulfurating reagent for sulfur atom transformation.[9] Inspired by this finding, one of the sulfur atoms exhibiting low-valence (-2) in thiosulfate was supposed to be oxidized by an appropriate high-valent sulfide (+6 or +4)[10] to achieve unsymmetrical disulfide (+1) via comproportionation, which may avoid poor selectivity of unsymmetrical persulfuration (Scheme 2, eq. 4). Certainly, other valent byproduct generation should be purposely avoided through control conditions.

We commenced with this hypothesis by testing different high-valent sulfur precursors reacting with alkyl thiosulfate formed *in situ*. To our satisfaction, the desired product was isolated in 6% yield when tosylchloride was employed as a reacting partner (Table 1, Entry 1). When 4-methylbenzenesulfonhydrazide, another S(VI) reagent, was applied, the reaction system was complicated (Table 1, Entry 2). The yield of the desired unsymmetrical disulfide was raised

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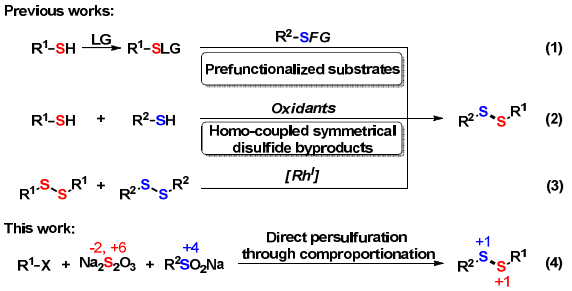
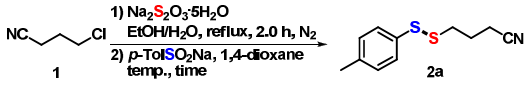


Scheme 2. Strategies for disulfide construction.

to 72% when employing sodium 4-methylbenzenesulfinate as the coupling partner (Table 1, Entry 3). The lower temperature (70 °C) gave an unsatisfactory yield (37%) (Table 1, Entry 4). In contrast, the reaction was improved to afford the **2a** in 88% yield by increasing the temperature (110 °C, reflux, Table 1, Entry 5). However, shortening or prolonging the reaction time did not enhance the yield (Table 1, Entries 6-8). Further study revealed that quenching the reaction with tri-phenylphosphine[11] produced a better result (94%, Table 1, Entry 9). When the prepared alkyl thiosulfate (Bunte salts)[12] was used instead of sodium thiosulfate/alkyl halide, the reaction became slightly sluggish in 69% yield (Table 1, Entry 10). Neither sodium sulfide nor sulfur(0)[13] could replace sodium thiosulfate in the reaction, which demonstrated the uniqueness of sodium thiosulfate again[9] in this transformation (Table 1, Entries 11-12). In addition, using benzyl mercaptan or 4-methoxybenzenethiol as sulfur partners could not afford unsymmetrical disulfide (Table 1, Entries 13-14).

Table 1. Optimization of persulfuration.[a]

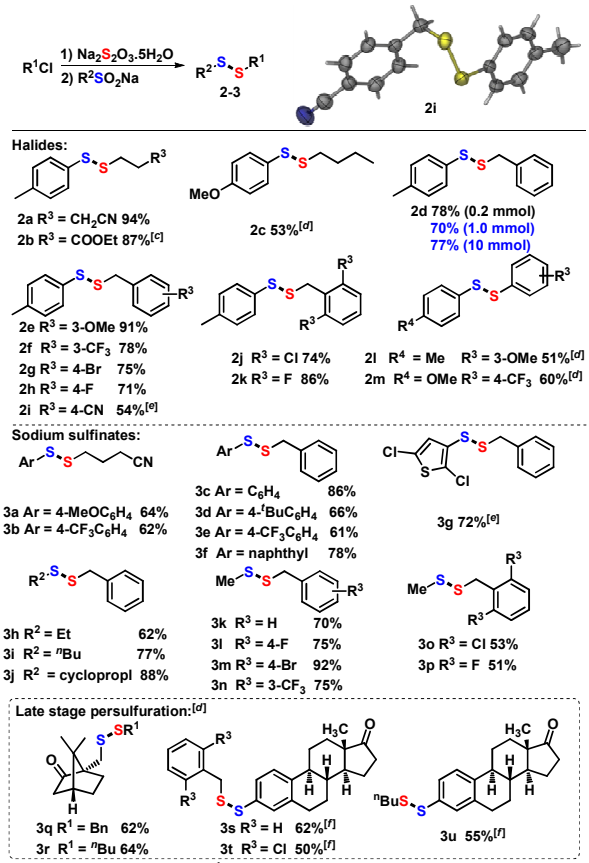


Entry	High-valent S Source	Low-valent S Source	Temp./°C	Time/h	Yield/%[b]
1	TsCl	$Na_2S_2O_3·5H_2O$	90	11	6
2	$TsNHNH_2$	$Na_2S_2O_3·5H_2O$	90	11	complicated
3	$TolSO_2Na$	$Na_2S_2O_3·5H_2O$	90	11	72
4	$TolSO_2Na$	$Na_2S_2O_3·5H_2O$	70	11	37
5	$TolSO_2Na$	$Na_2S_2O_3·5H_2O$	reflux	11	88
6	$TolSO_2Na$	$Na_2S_2O_3·5H_2O$	reflux	5	66
7	$TolSO_2Na$	$Na_2S_2O_3·5H_2O$	reflux	8	83
8	$TolSO_2Na$	$Na_2S_2O_3·5H_2O$	reflux	15	60
9	***$TolSO_2Na$***	***$Na_2S_2O_3·5H_2O$***	***reflux***	***11***	***94***[c]
10	$TolSO_2Na$	$R^1S_2O_3Na$	reflux	11	69[d]
11	$TolSO_2Na$	$Na_2S·9H_2O$	90	11	NR
12	$TolSO_2Na$	S_8	90	11	NR
13	$TolSO_2Na$	BnSH	90	11	NR[e]
14	$TolSO_2Na$	4-MeOPhSH	90	11	NR[e]

[a] Reaction conditions: **1** (1.0 mmol) and $Na_2S_2O_3·5H_2O$ (1.0 mmol) were added to EtOH/H_2O (0.25 mL/0.5 mL) at reflux for 2.0 h under N_2 atmosphere, then the solvent was removed. After adding $TolSO_2Na$ (0.2 mmol, 1.0 equiv.) and 1,4-dioxane (1.0 mL), the system was refluxed for 11 h. [b] Isolated yields. [c] After step 2, PPh_3 (0.12 mmol, 0.6 equiv.) was added. [d] $NCCH_2CH_2CH_2S_2O_3Na$ was used instead of halide **1** and $Na_2S_2O_3·5H_2O$. [e] BnSH or 4-MeOPhSH was used instead of halide **1** and $Na_2S_2O_3·5H_2O$.

Based on the optimized conditions, the substrate scope was diffusely investigated. First, various halides were tested. Unactivated halides, substituted with cyano (Table 2, **2a**) and ester (Table 2, **2b**), alkyl (Table 2, **2c**) groups could afford the corresponding disulfides in moderate to excellent yields. When activated halides were investigated in reaction, benzylic halides bearing both electron-donating and -withdrawing groups (Table 2, **2e-2f**), could proceed smoothly. Halogen atoms were tolerated in the reaction (Table 2, **2g-2h**, **2j-2k**). It is worth noting that even 2, 6-disubstituted benzyl halides were efficient partners (Table 2, **2j-2k**), as well. Moreover, unsymmetrical aryl-aryl disulfides were obtained by utilizing preformed aryl thiosulfate[14] (Table 2, **2l-2m**). To further determine practical utility, gram-scale operation was performed by applying 10 mmol of sodium 4-methylbenzenesulfinate, which afforded the desired product in good yield (77%, 1.9 grams) (Table 2, **2d**). The structure of **2i** was confirmed by X-ray analysis.[15]

Table 2. Scope of persulfuration.[a,b]



[a] Standard conditions: R^1Cl (1.0 mmol) and $Na_2S_2O_3·5H_2O$ (1.0 mmol) were added to EtOH/H_2O (0.25 mL/0.5 mL) at reflux for 2.0 h under N_2 atmosphere, then the solvent was removed. After adding $TolSO_2Na$ (0.2 mmol, 1.0 equiv.) and 1,4-dioxane (1.0 mL), the system was refluxed for 11 h. [b] Isolated yields. [c] R^1Br was used instead of R^1Cl. [d] $R_1S_2O_3Na$ was used instead of R^1Cl and $Na_2S_2O_3·5H_2O$. [e] 90 °C at step 2. [f] Sulfinate of estrone derivatives was used.

Various types of sulfinates were then studied extensively. As shown in Table 2, aryl sulfinates substituted with electron-withdrawing and -donating groups (Table 2, **3a-3e**) gave the desired products in good yields. Sulfinates on heterocycle and condensed ring performed successfully (Table 2, **3f-3g**). The method could be applied with alkyl sulfinates, as well (Table 2, **3h-3p**). Considering the great attention to biologically active natural products substituted

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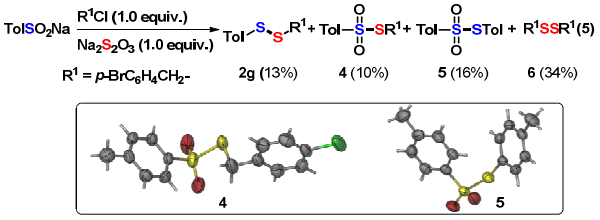
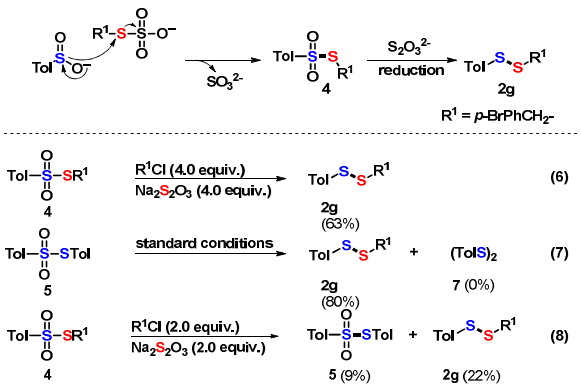
with methyl disulfides[8] and the limitation of preparing methyl disulfides, sodium methanesulfinate was deliberately employed. Substituted benzylic halides worked smoothly with sodium methanesulfinate (Table 2, **3k-3p**), in which a batch of methyl substituted disulfides were synthesized. Furthermore, this reaction could be smoothly applied in the late stage persulfuration of pharmaceuticals and natural products (Table 2, **3q-3u**), which offered a convenient method for drug modification. Importantly, camphorsulfonic acid and estrone derivatives exhibited persulfuration in this transformation without erosion of stereogenic information.

On the basis of these results, the mechanism of this transversion was explored. From the ratio of two different sulfur source points, the relationship between the amounts of thiosulfate and yields of unsymmetrical disulfide were investigated (see ESI†). According to the results, disulfide formation was less than half when less than two equivalents of sodium thiosulfate/halide were added. The yield increased to 68% after three equivalents of thiosulfate/halide were loaded. Furthermore, the highest yield (75%) was achieved when five equivalents of thiosulfate/halide were added. However, the yield increased slightly when three equivalents of thiosulfate/halide were utilized, which indicated that three equivalents of thiosulfate/halide constituted the necessary amount for comproportionative completion. Two side products **4** (10%) and **5** (16%) were isolated, whose structures were confirmed by X-ray,[16, 17] as well as **6** (34%), when one equivalent of thiosulfate/halide was applied in the reaction (Scheme 3, eq. 5). Neither compound **4** nor **5** was detected in the reaction system when more than two equivalents of thiosulfate/halide were added. This information supports that thiosulfate serves both as the sulfur source and reductant of the reaction.



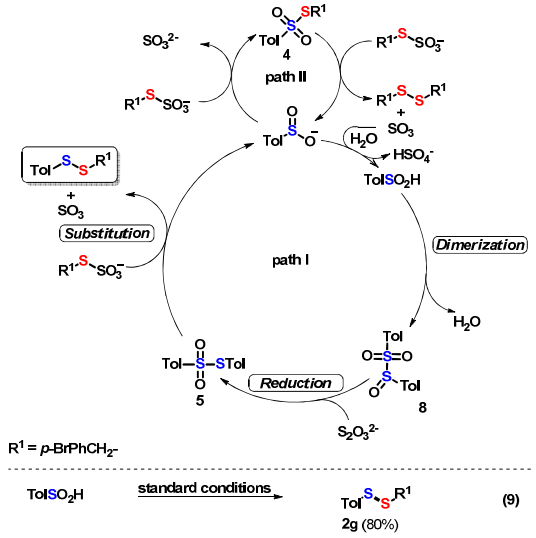
Scheme 3. X-ray of intermediate **4** and **5**.

The first proposed S_N2 attacking mechanism was suggested in Scheme 4. S-4-bromobenzyl 4-methylbenzenesulfon-othioate **4** was formed by the attack from sulfinate to alkyl thiosulfate, which was subsequently reduced by excess thiosulfate to afford the disulfide. To validate this explanation, intermediate **4** was treated with four equivalents of thiosulfate, which provided unsymmetrical disulfide **2g** in 63% yield (Scheme 4, eq. 6). On the other hand, the compound **2g** was obtained in 80% yield when S-*p*-tolyl 4-methylbenzenesulfonothioate **5** (0.1 mmol of **5** was used) was tested under standard conditions. However, the symmetrical disulfide **7**, which was supposed to be the reductive product, was not detected in the reaction system (Scheme 4, eq. 7). This indicates that the S_N2 process between sulfinate and thiosulfate occurred much faster than the reductive process. Moreover, the reductive process might be unreasonable during the transformation of intermediate **4** to product **2g**. Therefore, compound **5** seemed to be a crucial intermediate of the reaction. Notably, when intermediate **4** was treated with insufficient thiosulfate/halide (two equivalents), 9% of intermediate **5** was isolated, as well as 22% of unsymmetrical disulfide **2g** (Scheme 4, eq. 8), which indicates that compound **4** may convert to intermediate **5** first, and then transform to unsymmetrical disulfide **2g**.



Scheme 4. Proposed S_N2 attacking process and control experiments.

Therefore, another mechanism was suggested in Scheme 5. Firstly, tosyl *p*-tolyl sulfone **8** was generated through the dimerization of 4-methylbenzenesulfinate under acidic conditions[18] (due to the sulfur trioxide generating from substitution of the alkyl thiosulfate). Then, compound **5** could be produced by **8** through reduction of thiosulfate. Intermediate **5** was then attacked by alkyl thiosulfate to afford the unsymmetrical disulfide and a molecule of 4-methylbenzenesulfinate, which could be explained by equation 7 (Scheme 5, path I).[19] To further prove this pathway, 4-methylbenzene-sulfinic acid was conducted as a replacement under the standard conditions. As a result, the desired product **2g** was isolated in 80% yield (Scheme 5, eq. 9). Meanwhile, the sulfinate could be attacked by alkyl thiosulfate to afford the S-4-bromobenzyl 4-methylbenzenesulfonothioate **4**, which might be attacked again to regenerate sulfinate (Scheme 5, path II). This pathway explained the formation of intermediate **5** and unsymmetrical disulfide **2g** when product **4** was used as the substrate (Scheme 4, eq. 6 and 8). In summary, thiosulfate played the roles of sulfur source, reductant, and acidic condition supplier in the whole process. Symmetric disulfide was speculated to be produced in the process of reduction as an oxidative byproduct.



Scheme 5. Proposed mechanism and control experiments.

In conclusion, we have reported a novel method to achieve various kinds of unsymmetric disulfides efficiently, including methyl disulfides and derivatives of natural products, by comproportionation between sulfinates and thiosulfates, which are characterized by odorlessness, economic feasibility, and

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practicality. Neither extra oxidant nor reductant was needed in this transition-metal-free reaction, which made this chemistry environmentally friendly. Furthermore, an unusual sulfur redox process was revealed. Key isolated intermediates and a series of control experiments provided an outline of the reaction mechanism, in which thiosulfate played the roles of sulfur source, reductant, and acidic condition supplier in the whole process. Further studies of synthetic applications to other disulfide-containing natural products and persulfuration of drugs are ongoing.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data for all new compounds. CCDC 1017450, 1017451, and 1017452. For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/c000000x/

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